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ELSEVIER SCIENCE FULL-TEXT ARTICLE

Metalloproteinase inhibitor prevents hepatic injury in endotoxemic mice.

Murakami K, Kobayashi F, Ikegawa R, Koyama M, Shintani N, Yoshida T, Nakamura N, Kondo T.

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This study was conducted to examine of [4-(N-hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide (GI 129471), a matrix metalloproteinase inhibitor, for its effects on increase of serum pro-inflammatory cytokine levels as well as hepatic injury in D-galactosamine plus lipopolysaccharide-injected mice. In vitro experiments showed that GI 129471 was able to inhibit the elevation of tumor necrosis factor-alpha (TNF-alpha) in LPS-stimulated human and mouse whole blood with IC50 values of 370 nM and 260 nM, respectively. When administrated i.p. at 40 mg/kg, GI 129471 significantly reduced serum TNF-alpha level but not other pro-inflammatory cytokines in D-galactosamine plus lipopolysaccharide-injected mice. Treatment of mice with GI 129471 also reduced biochemical indices of hepatic injury to the normal level. Histopathological findings indicated that GI 129471 treatment can prevent severe centrilobular necrosis in liver. These results suggest that release of TNF-alpha from lipopolysaccharide-stimulated cells is the critical step leading to hepatic injury in endotoxemia and that a matrix metalloproteinase inhibitor with an inhibitory action on this step may be a promising drug for the clinical treatment of endotoxemia accompanied by hepatic injury.

PMID: 9489862 [PubMed - indexed for MEDLINE]

1: J Gastrointest Surg 2000 Sep-Oct;4(5):536-41 Related Articles, Books, LinkOut

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Matrix metalloproteinase inhibition protects hepatic integrity in hemorrhagic shock.

Santibanez-Gallerani AS, Barber AE, Williams SJ, Davis S, Zhao Y, Shires GT.

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Hemorrhagic shock increases cytokines, such as tumor necrosis factor-alpha (TNF-alpha), and interleukin-6 (IL-6), and compromises hepatic function and integrity. The production of TNF-alpha involves a cascade reaction regulated by the enzyme TNF-alpha convertase. The purpose of this study was to examine the effects of matrix metalloproteinase inhibitor (MMPI) (British Biotech 1101) in vivo on hepatic integrity in a rat model of hemorrhagic shock. Sprague-Dawley rats (n = 26) were divided as follows: hemorrhagic shock (group 1) and hemorrhagic shock plus MMPI (group 2). TNF-alpha, IL-6, and hepatic membrane potentials (Em) were obtained. The administration of MMPI significantly decreased TNF-alpha levels ($P < 0.001$) and stabilized the membrane potential at -30 mV as compared to the depolarized membrane potential at -20 mV for hemorrhagic shock without MMPI. IL-6 levels were not affected by the MMPI. This study demonstrates that MMPI decreases TNF-alpha levels and protects hepatic integrity in hemorrhagic shock, as evidenced by the stabilization of the membrane potential, independent of the mean arterial pressure. The hepatic protection is closely related to the decrease in TNF-alpha levels seen in the portal circulation.

PMID: 11077331 [PubMed - indexed for MEDLINE]

1: Br J Haematol 1999 Apr;105(1):303-12

online

A metalloproteinase inhibitor prevents acute graft-versus-host disease while preserving the graft-versus-leukaemia effect of allogeneic bone marrow transplantation.

Hattori K, Hirano T, Miyajima H, Yamakawa N, Ikeda S, Yoshino K, Tateno M, Oshimi K, Kayagaki N, Yagita H, Okumura K.

Division of Haematology, Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan.

We examined the effect of a hydroxamic acid-based matrix metalloproteinase inhibitor (KB-R7785), which we previously demonstrated to have a potent ameliorating effect on acute graft-versus-host disease (GVHD), and on the graft-versus-leukaemia (GVL) effect of allogeneic bone marrow transplantation (BMT). KB-R7785 was administered to (C57BL/6 x BALB/c) F1 (CBF1) mice that had been inoculated with IgE-producing B53 hybridoma cells of BALB/c origin as a model tumour, along with or without transplantation of C57BL/6 (B6) bone marrow cells and spleen cells (BMS). Administration of KB-R7785 without BMS significantly prolonged the survival of B53-inoculated CBF1 mice by inhibiting the infiltration of B53 cells into the liver and spleen. Transplantation of B6 BMS without KB-R7785 resulted in the death of most recipients due to acute GVHD while efficiently eliminating B53 cells. Administration of KB-R7785 along with B6 BMS resulted in a 50% survival of B53-inoculated CBF1 mice over 50 d without histological manifestations of acute GVHD or residual B53 cells. These results indicate the beneficial effects of KB-R7785 that inhibit tumour infiltration and prevent acute GVHD while preserving the GVL effect of allogeneic BMT.

PMID: 10233398 [PubMed - indexed for MEDLINE]

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Administration of a matrix metalloproteinase inhibitor after hemorrhage improves cardiovascular and hepatocellular function.

Wang P, Ba ZF, Galardy RE, Chaudry IH.

Center for Surgical Research, Brown University School of Medicine, Providence, Rhode Island, USA.

Although matrix metalloproteinase inhibitors prevent the increase in soluble tumor necrosis factor-alpha during endotoxemia, it remains unknown whether a novel matrix metalloproteinase inhibitor, GM6001, improves cardiovascular and hepatocellular function after trauma and hemorrhage. To determine this, rats underwent laparotomy (i.e., trauma-induced), and were bled to and maintained at a mean arterial pressure of 40 mmHg until 40% of maximal shed volume was returned in the form of Ringer's lactate. The animals were then resuscitated with 3 times the volume of maximal bleedout with Ringer's lactate over 45 min, followed by 2 times Ringer's lactate over 60 min. GM6001, at a dose of 100 mg/kg or an equal volume of normal saline, was administered subcutaneously 15 min before the completion of resuscitation. At 2 and 4 h after resuscitation, cardiac output was measured by indocyanine green (ICG) dilution. Hepatocellular function (i.e., maximum velocity and the efficiency of ICG clearance) was determined by in vivo ICG clearance. Microvascular blood flow in various organs was assessed by laser Doppler flowmetry. The results indicate that cardiac output, hepatocellular function, and tissue microvascular blood flow decreased significantly at 2 and 4 h after resuscitation. GM6001 treatment, however, significantly improved the depressed cardiovascular and hepatocellular function. Since GM6001 improves cardiovascular and hepatocellular function, this agent may be a useful adjunct to fluid resuscitation after trauma and hemorrhagic shock.

PMID: 8946655 [PubMed - indexed for MEDLINE]

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Matrix metalloproteinase inhibitor BB-94 (batimastat) inhibits human colon tumor growth and spread in a patient-like orthotopic model in nude mice.

Wang X, Fu X, Brown PD, Crimmin MJ, Hoffman RM.

AntiCancer, Inc., San Diego, California 92111.

Matrix metalloproteinases have been implicated in the growth and spread of metastatic tumors. This role was investigated in an orthotopic transplant model of human colon cancer in nude mice using the matrix metalloproteinase inhibitor BB-94 (batimastat). Fragments of human colon carcinoma (1-1.5 mm) were surgically implanted orthotopically on the colon in 40 athymic nu/nu mice. Administration of BB-94 or vehicle (phosphate buffered saline, pH 7.4, containing 0.01% Tween 80) commenced 7 days after tumor implantation (20 animals/group). Animals received 30 mg/kg BB-94 i.p. once daily for the first 60 days and then 3 times weekly. Treatment with BB-94 caused a reduction in the median weight of the primary tumor from 293 mg in the control group to 144 mg in the BB-94 treated group ($P < 0.001$). BB-94 treatment also reduced the incidence of local and regional invasion, from 12 of 18 mice in the control group (67%) to 7 of 20 mice in the treated group (35%). Six mice in the control group were also found to have metastases in the liver, lung, peritoneum, abdominal wall, or local lymph nodes. Only two mice in the BB-94 group had evidence of metastatic disease, in both cases confined to the abdominal wall. The reduction in tumor progression observed in the BB-94-treated group translated into an improvement in the survival of this group, from a median survival time of 110 days in the control group to a median survival time of 140 days in the treated group ($P < 0.01$). Treatment with BB-94 was not associated with any obvious toxic effect, and these results suggest that such agents may be effective as adjunctive cancer therapies.

PMID: 8062271 [PubMed - indexed for MEDLINE]

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1: Cancer Res 1995 Aug 15;55(16):3629-33 Related Articles, Books, LinkOut

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Inhibition of organ invasion by the matrix metalloproteinase inhibitor batimastat (BB-94) in two human colon carcinoma metastasis models.

Watson SA, Morris TM, Robinson G, Crimmin MJ, Brown PD, Hardcastle JD.

Department of Surgery, Queen's Medical Centre, University Hospital, Nottingham, United Kingdom.

The effect of the matrix metalloproteinase inhibitor batimastat was evaluated in two human colorectal cancer metastasis models involving: (a) the liver-invasive tumor C170HM2 and (b) the lung-invasive tumor AP5LV, both of which have been shown to express the M(r) 72,000 type IV collagenase. Batimastat at concentrations between 0.01 and 3.0 micrograms/ml had no direct cytotoxic effects on the in vitro growth of the cell lines. In the liver-invasive tumor model, batimastat administered i.p. from day 10 to termination of the therapy (day 39) at 40 mg/kg reduced both the mean number of liver tumors (35% of vehicle-treated control; $P < 0.05$) and the cross-sectional area of the tumors (43% of vehicle-treated control; $P < 0.05$). In the lung-invasive tumor model, batimastat administered daily (40 mg/kg i.p.) significantly reduced tumor weight within the lung (72% of vehicle-treated control; $P < 0.05$) but did not significantly affect nodule number. In the latter model, in which the take rate was unaffected, tumor cells were introduced into the lateral tail vein, and lung localization may have been a physical phenomenon not involving invasion. In the former model, tumor cells were introduced directly into the peritoneal cavity, and from there the cells adhered to and invaded the liver capsule. Because the take rate is significantly reduced, it may be that the matrix metalloproteinases are involved in this process. Batimastat may be a therapeutic modality for the treatment of colorectal cancer metastasis.

PMID: 7627972 [PubMed - indexed for MEDLINE]

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